

# Meeting the Challenge

An update on the ATTRACT trial.

BY SURESH VEDANTHAM, MD

**T**he ATTRACT (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis) trial is sponsored by the National Institutes of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) and is a phase-3, open-label, assessor-blind, multicenter, randomized controlled trial (RCT) that will determine whether the routine use of adjunctive pharmacomechanical catheter-directed thrombolysis (PCDT) can prevent postthrombotic syndrome (PTS) in patients with symptomatic, acute, proximal deep vein thrombosis (DVT). The ATTRACT trial will randomize 692 patients to receive either PCDT plus standard DVT therapy (anticoagulant therapy and elastic compression stockings) or standard DVT therapy alone.

Patients will have follow-up visits at 10 and 30 days and at 6, 12, 18, and 24 months after randomization to assess the presence and/or severity of PTS (using the Villalta scale, VCSS [venous clinical severity score], and CEAP [clinical, etiologic, anatomic, pathophysiologic measures]),<sup>1-5</sup> generic and venous disease-specific quality of life (using SF-36 and VEINES-QOL measures, respectively),<sup>6,7</sup> relief of presenting symptoms (assessed using a Likert pain scale and calf circumference measurements), safety (bleeding, recurrent venous thromboembolism, death), cost effectiveness, and ultrasound imaging endpoints (valvular reflux and residual thrombus).

## ARE GREAT GENES ENOUGH?

The ATTRACT research team is proud of the trial's design not because it is a study promoting catheter-based intervention but because it is a far-reaching, multidisciplinary collaboration of the DVT research community that is seeking to address an important public health problem. The ATTRACT leadership includes DVT

research leaders from interventional radiology, vascular surgery, cardiology, pulmonary medicine, epidemiology, hematology, economics, and biostatistics. The study's Clinical Coordinating Center (CCC) is based at the Mallinckrodt Institute of Radiology at Washington University School of Medicine in St. Louis, Missouri. The Ontario Clinical Oncology Group at McMaster University in Hamilton, Ontario, Canada, a renowned clearinghouse for DVT trials, serves as the ATTRACT trial's Data Coordinating Center and provides important methodological and biostatistical expertise to the study. Core laboratories in vascular ultrasound (VasCore at the Massachusetts General Hospital in Boston) and health economics (St. Luke's Mid America Heart Institute in Kansas City, Missouri) coordinate an ultrasound substudy and a cost comparison, respectively.

Each of the 50 ATTRACT clinical centers fields a diverse investigator team that includes an endovascular physician, a medical physician, an emergency department physician, and the vascular ultrasound laboratory director at a minimum, of whom many are national DVT research leaders. The trial is primarily sponsored by the NHLBI and receives additional support from four industry partners: BSN Medical (Charlotte, NC) (donating compression stockings), Covidien (Mansfield, MA) (donating funds), Genentech, Inc. (San Francisco, CA) (donating recombinant tissue plasminogen activator), and Medrad Interventional/Possis (Indianola, PA) (donating funds). The Society of Interventional Radiology (which played an important role in trial development), the American Venous Forum, and the American College of Phlebology stand together in public support of the trial.

The ATTRACT trial features the use of two PCDT methods that have spurred excitement within the endovascular community: the isolated thrombolysis

technique (using the Trellis peripheral infusion system [Bacchus Vascular, Santa Clara, CA]) and the power pulse technique (using the AngioJet rheolytic thrombectomy system [Medrad Interventional/Possis]). Both techniques enable thrombolytic therapy for DVT to be completed in a single, on-table procedure session, potentially reducing the risks and costs of therapy.<sup>8-11</sup>

Finally, the United States government health agencies stand firmly behind the study. The NHLBI funds approximately \$10.2 million to the study. At the June 2009 ATTRACT Investigator Meeting, Assistant United States Surgeon General James M. Galloway publicly highlighted the trial's importance to the public health, as well as the Surgeon General's strong support for its completion.<sup>12</sup>

To summarize, the ATTRACT trial would seem to have great "genetic" composition, and therefore, one might conclude that its success is assured. But this would be a mistake; in fact, both distant and recent history provide little basis for complacency. The challenges faced by DVT thrombolysis trials are substantial, and patient recruitment to such studies has been very difficult.<sup>13</sup> In previous reviews of enrollment to RCTs of systemic thrombolysis for DVT, less than 20% of screened patients were found to meet study eligibility criteria. More recently, two multicenter trials (including the ambitious, well-designed TOLEDO study) and a prospective cohort study were terminated in part due to the inability to recruit patients in a timely fashion.

## CURRENT STATUS OF STUDY START-UP

The start-up process for the ATTRACT trial has been slow, which is as expected for a complex, 50-site NIH trial. Issues that have delayed the start of study enrollment have included: (1) the extended time (3–12 months) for sites to process the study contracts, which may have been prolonged by the large number of 2009 Recovery Act NIH grant applications (given priority in most institutions); (2) the NHLBI's decision in mid-2009 to put the study on hold for several months to change the format of its Data Safety Monitoring Board before subject enrollment; (3) and the Steering Committee's decision, based on investigator feedback at the investigator meeting, to amend the protocol in several ways, which increased its ease of use at the clinical centers.

To date, there are 41 fully activated sites in the ATTRACT trial (many activated during the second quarter of 2010) and an additional 15 to 20 sites in various stages of start-up. Through June 23, 2010, a total of 41 patients have been enrolled at 17 different sites. The good news is that of the patients who met all eligibility criteria, approximately 40% have agreed to participate.

On the other hand, study-wide, approximately 30 patients have been screened per patient enrolled. Together, these findings suggest that the study is indeed feasible but only with aggressive efforts to promote enrollment.

## CREATING A NEW PROFESSIONALISM IN ENDOVASCULAR DVT RESEARCH

The ATTRACT trial falls into the general category of "medical therapy versus surgical therapy" trials. In such studies, patients are asked to allow a research team (via randomization) to determine which of two drastically different treatment approaches they will receive, and in ATTRACT, allocation to one treatment arm involves one to three invasive procedures, a hospital stay, and significant up-front risk. To complicate matters further, both treatment options are offered outside the study, so access to a "new" treatment cannot effectively be used as a selling point. For such studies to succeed, strong support from a motivated coordinating center is essential. The ATTRACT CCC is providing all active sites with resources including brochures (in English and Spanish), posters, protocol cards, "Dear Colleague" letter templates, funds to cover the work efforts of screening large volumes of patients, a 24/7 telephone hotline, an interactive study Web site with enrollment tips, a Patient Recruitment Strategy Guide, and other resources.

But beyond that, success in the ATTRACT trial will require its participating endovascular physicians to reach for a higher level of "research professionalism" than they may be accustomed to, one that matches that possessed by medical thrombosis researchers, who often conduct far simpler studies (eg, comparing two different durations of warfarin therapy). The reality is that even academic interventional radiologists and vascular surgeons tend to be trained first and foremost as clinicians. In such training programs, little time is spent on learning about clinical trials methodology, study implementation, and strategies to boost patient recruitment. This differs greatly from internal medicine programs, in which training to participate successfully in clinical trials is part of the culture. The success of ATTRACT will depend on the degree to which endovascular investigators can change their culture and thinking in the ways explained in the following sections.

## Recognize Clinical Trial Recruitment as a Distinct Activity

The ATTRACT endovascular physicians have been successful in building their clinical DVT thrombolysis practices. However, building a practice is very different

from recruiting patients to a clinical trial. To build a clinical practice, one needs to convince patients and physicians that the long-term risks of PTS should favor an aggressive treatment approach. However, most patients referred in this manner were initially treated with anticoagulant therapy alone but exhibited symptom progression that ultimately prompted the physician to refer and the patient to want a more aggressive therapy. Most such patients have concluded that standard therapy is insufficient and will not agree to be randomized to the control arm (no lysis), and many would be excluded anyway due to symptom duration exceeding 2 weeks or due to other contraindications. In contrast, successful recruitment to ATTRACT requires identification of DVT patients when they are initially diagnosed, before they have formed an opinion on the effectiveness of anticoagulant therapy alone. This requires an entirely different approach based on identification of large numbers of DVT patients in the vascular ultrasound laboratory, emergency room, and other primary care settings. This will require more effective collaboration between endovascular physicians and the gatekeeper DVT physicians who have direct access to presenting DVT patients. Although the Steering Committee has tried to foster these partnerships, it will ultimately be up to the site investigators to cultivate them throughout the study period.

## Embrace Clinical Equipoise

Only in 2008 did elective DVT thrombolysis become an acceptable practice in the published guidelines followed by the medical physicians who determine initial DVT care.<sup>14</sup> During many years performing these procedures, endovascular physicians have become accustomed to providing a “hard sell” in terms of arguing that the long-term risks of severe PTS mitigate in favor of the use of PCDT. However, in ATTRACT, a patient can choose either therapy outside the study, so overselling the intervention actually discourages enrollment in the study. In fact, many endovascular physicians quote excessively high numbers for the expected rates of PTS and venous ulceration that reflect outdated studies performed in highly selected patient populations. Modern prospective studies using validated outcome measures certainly confirm that PTS is very common (25%–50% of patients with proximal DVT) but that venous ulcers are infrequent, making it unclear whether the risks and costs of PCDT should be routinely incurred.<sup>15–18</sup>

In addition, physicians generally have strong opinions about whether PCDT is appropriate in specific patients. Most endovascular physicians cringe at the idea of randomizing a 21-year-old woman with left iliofemoral DVT

from May-Thurner syndrome to the control arm of an RCT. Similarly, most internists would not think of using PCDT for a 70-year-old man with a femoropopliteal DVT who had a gastrointestinal bleed 4 months ago.

However, the trial may be inappropriately negative if the first patient who seems likely to benefit the most from PCDT is kept out. It is important that the study's results can be extrapolated to patients similar to the second patient mentioned because they will be treated with PCDT in clinical practice if the study is positive. Therefore, physicians need to refine their rhetoric and adopt the language of clinical equipoise with patients, recognizing that the same patient is often viewed very differently by physicians across the spectrum.

## Actively Seek Available Clinical Research Resources

Most academic institutions and many large private hospitals have a research infrastructure that exists to enhance recruitment to clinical trials. One example is an NIH Clinical and Translation Science Award (CTSA) program, which usually provides a number of invaluable, free recruitment resources to investigators. However, few vascular surgeons, and even fewer interventional radiologists, are plugged in to their institution's research resources. It is essential for the ATTRACT investigators to actively seek out and liberally use such resources. For example, the CCC discovered that 13 ATTRACT sites have CTSA programs. In communicating this to the site investigators, it became clear that very few even knew of their CTSA's existence.

## CONCLUSION

In the United States, it is so often true that advances in knowledge and technology far outpace the ability of our heterogeneous, complicated medical system to actually deliver this knowledge and technology to patients in a manner that improves health outcomes. The failure to implement these represents the fundamental Achilles' heel of the United States health enterprise and is particularly applicable to endovascular DVT research. In 2010, the endovascular DVT physician community finds itself at a critical juncture, one that requires a veritable culture change in the way we have approached the research aspect of our practices. The importance of the ATTRACT trial to DVT patients is widely recognized, but success will require endovascular physicians to collectively raise their game as research professionals. It is hoped that this creative evolution will represent another way in which the ATTRACT trial pushes the DVT research paradigm forward to enable the next generation of endovascular therapies to be

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industry "courses" highlight other aspects of venous disease (diagnosis, treatment, practice management, etc.). Many courses and training sessions/videos are given by thought leaders in the venous field. A physician should use industry's knowledge and experience, and with an appropriate perspective, this interaction can further a practitioner's knowledge base. Industry should be commended for their support not only with its own courses but also with its committed involvement to the main venous societies, PVF and ACP. Without industry's help, many of the societal venous initiatives would not be as successful as they are.

## INTERVENTIONISTS

I suggest that anyone interested in learning more about treating venous disease talk to those of us who have been involved and have specialized in the field. Many of us treat venous disease exclusively; other thought leaders have vein disease treatment as a large part of their practice. We enjoy teaching the educational process and want to help. Realize that this process takes time, effort, and commitment. Even though veins and arteries both carry blood, that is about where the similarity ends. Most of us were not lucky enough to get a lot of training in venous disease during residency or fellowship; we learned on the job. In 2010, I think we have created a number of good educational pathways for others. Realize that your education in a new specialty, phlebology, will take more time and effort than continuing education in your present specialty.

## CONCLUSION

If there is something you did not learn during your academic training, it is much harder to learn once you are practicing. Know your options and areas of need, as well as the time, effort, and money needed to pursue further venous education. I feel that in 2010, there are a multitude of options that we have developed so that you can find what is best for you. If I can be of any help, feel free to contact me directly. ■

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evaluated with the same skill and resources from which clinical studies of conventional pharmacological interventions routinely benefit. ■

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